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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/076,248	02/12/2002	Lloyd G. Mitchell	A31304-B-A-F 069906.0105	6317

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EXAMINER	
WILDER, CYNTHIA B	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 01/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/076,248	MITCHELL ET AL.	
	Examiner	Art Unit	
	Cynthia B. Wilder, Ph.D.	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34 and 36-53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-30,36-47 and 50-52* is/are rejected.

7)☒ Claim(s) *31-34,48,49 and 53* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 July 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I. Claims 1-33 and 36-53 in the reply filed on 11/8/2004 is acknowledged. The restriction requirement as set forth in the previous office action is withdrawn in view of Applicant's arguments. Claim 35 has been canceled. Claims 1-34 and 36-53 are pending and addressed in this Office Action.

2. Applicant's preliminary amendment file on July 26, 2002 is acknowledged and has been entered.

Priority

3. On page 1 of the specification as filed and in the Oath and Declaration, Applicant states that the filing date of the provisional application number 60/008,317 is December 15, 1995. According to PTO records the filing date should state December 7, 1995.

Claim Objections

4. Claims 31-34, 48, 49 and 53 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only and/or cannot depend from any other multiple dependent claims. See MPEP § 608.01(n). Accordingly, the claims 31-34, 48, 49 and 53 have not been further treated on the merits.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-30, 36-47, 50-52 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for producing chimeric RNA molecule using the modified synthetic nucleic acids molecules in a cell *in vitro*, it does not reasonably provide enablement for producing chimeric RNA molecules using the modified synthetic nucleic acid molecules *in vivo* for therapeutic treatment of various diseases and conditions and regulation of gene expression in a cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The first paragraph of section 112 requires the specification describe how to make and use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is "undue". These factors include but are not limited to: (1) quantity of experimentation necessary, (2) the amount of direction or guidance presented in the specification, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability of the unpredictability of the art and (8) the breadth of the claims. (See *In re Wands*, 858 F. 2d 731, 8 USPQ2d 1400, 1404, (Fed. Cir. 1988)) *(MPEP 2164.01(a))*.

The instant invention is drawn to a modified synthetic nucleic acid molecule and expression vector, wherein said modification enhances the stability of the nucleic acid molecule comprising: one or more target binding domains that target binding of the nucleic acid molecule to a pre-mRNA expressed within the cell; a 3' spliced region comprising a branch point, a pyrimidine tract and a 3' splice acceptor site or a 5' splice site and a nucleotide sequence to be

trans-spliced to be target pre-mRNA; wherein said nucleic acid molecule is recognized by nuclear splicing components within the cell, wherein said cell encompasses cells in a whole organism. The specification as filed provides only sufficient guidance and/or instruction for using the claimed synthetic nucleic acid construct to produce chimeric molecules within a cell in an in vitro environment, wherein said constructs are used to produce a chimeric mRNA. The specification as filed does not provide sufficient guidance such that the ordinary skilled artisan could use the teachings of the specification as filed as a guide to use the compounds of the instant claims to treat various diseases and conditions in a method of gene therapy.

There are a variety of factors that complicate the gene therapy art which have not been overcome by routine experimentation. These include, the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, et), the in vivo consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount of stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the vector used, the protein being produced the subject it is administered to, and the diseased being treated. Applicant states that additionally, the specification does not provide any working examples that enable the claimed invention. Nor does the specification provide any guidance to the skilled artisan on how to make and use genetic constructs that would result in the desired effect. Even assuming that an effective genetic material is constructed, it is not evident that enough cells can be transfected to provide any therapeutic benefits.

It is noted that the instant application claims priority back to December 15, 1995. However, it is noted that at the time the instant invention was made, the state of the prior art indicated that efficient delivery and expression of foreign DNA has not yet been achieved by any method. Marshall (Science. Vol. 269, pages 1050-1055, August 1995) states "there has been no unambiguous evidence that genetic treatment has produced therapeutic benefits" (page 1050, col. 1) and that "difficulties is getting genes transferred efficiently to target cells- and getting them expressed- remain a nagging problem for the entire field" (page 1054, col. 3). James Wilson, one skilled in the art, is quoted in the Marshall article as saying that "[t]he actual vectors- how we're going to practice our trade- haven't been discovered yet" (page1055, col. 2).

In the instant case, the quantity of experimentation required to practice the claimed invention would encompass determining means such that all pre trans-splicing molecules are all expressed in the same diseased cells at the same time and for a sufficient period of time such that the desired chimeric mRNA molecule is produced in a therapeutic amount to correct the defect in the diseased cells. Neither the specification as filed, nor the state of the prior art at the time the invention was made provides any specific guidelines in this regard. The deficiencies in specification would constitute undue experimentation since theses steps must be achieved without instruction from the specification before one is enable to practice the claimed invention.

Therefore, it is conclude that the amount of experimentation required for the skilled artisan to practice the full scope of the claimed invention would be undue based upon the know unpredictability regarding the efficient delivery of gene therapy constructs *in vivo* and further with the production of secondary effects such as treating a disease associated with the expression of a gene, and the lack of guidance in the specification as filed in this regard. The quantity of

experimentation required to practice the invention as claimed would require determining modes of delivery in a whole organism such that the expression of a single gene is replaced and the desired secondary effect is obtained. The specification as filed provides no specific guidelines in this regard. The deficiency in the specification would constitute undue experimentation sine these steps must be achieved without instructions from the specification before one is enable to practice the claimed invention.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-30, 36-47, 50-52 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 1-30, 36-47, 50-52 are drawn to a modified, synthetic nucleic acid molecule and expression vector. The modified synthetic nucleic acid molecule comprises one or more target binding domains that target binding of the nucleic acid molecule to a pre-MRNA expressed within the cell; a 3' spliced region comprising a branched point, a pyrimidine tract and a 3' splice acceptor site, 5' donor site and a nucleotide sequence to be trans-spliced to the target pre-mRNA; wherein said nucleic acid molecule is recognized by nuclear splicing components within the cell. The specification teaches at paragraph 0032 that the synthetic pre-trans-splicing molecules (modified synthetic nucleic acids) of the invention encompasses any cell type that

include, but is not limited to those infected with viral or other infectious agents, benign or malignant neoplasm or components of the immune system which are involved in autoimmune disease or tissue rejections. The specification further teaches (same paragraph) that the gene products encoded by the chimeric RNA can be any genes, including genes having clinical applications, for example, therapeutic genes, marker genes and genes encoding toxins. At paragraph 0035, the specification teaches the target binding domain of the synthetic pre-trans splicing molecule {PTM} (modified synthetic nucleic acid) is defined as any molecule, nucleotide, protein, chemical compound, etc., that confer specificity of binding and anchors the pre-mRNA closely in space to the synthetic PTM so that the spliceosomes processing machinery of the nucleus can be trans-splice a portion of the synthetic PTM to a portion of the pre-mRNA. The specification as filed does not teach the skilled artisan how to predict the structures of the full scope of "target biding domains" encompassed by the claims. The claims further encompasses any pre-mRNA expressed within any cell type isolated from any species which may be targeted by the one or more undisclosed target binding domains. Therefore, apart from further experimentation, the skilled artisan would not be able to predict the actual structural description of the full scope of the target binding domains that target binding of the nucleic acid molecules to a pre-mRNA expressed with any cell as encompassed by the instant claims.

See the January 5, 2001 (vol. 66, No.4, pages 1099-111) Federal Register for the Guidelines for Examination of Patent Applications Under the 35 USC 112 1, "Written Description" Requirement. The guidelines state that "[T]o satisfy the written description requirement, patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. An applicant

shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams and formulas that fully set forth the claimed invention. Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawing or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention.

Moreover, according to MPEP 2163, which states "a biomolecule sequence described only by a functional characteristic, without any know or disclosed correlation between that function and the structure of the sequence, normally is not sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence". In the instant cases, the specification as filed does not provide an adequate description of a modified synthetic nucleic acid as claimed. More specifically, the specification does not provide an adequate description of the target binding domains of the inventions, wherein said target binding domains target binding of the nucleic acid molecules to a pre-MRNA expressed within any cell type or species.

Double Patenting

9. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. Claims 1-30, 36-47, 50-52 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 19-34 of U.S. Patent No. 6013487. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F. 2d 887, 225 USPQ 645 (fed. Cir. 1985).

Although the conflicting claims are not identical, they are not patentably distinct from each other. Instant claims 1-30, 36-47, 50-52, and the claims 19-34 of US. Patent No. 6013487 are both directed to a nucleic acid comprising one or more target biding domains that target binding of the nucleic acid to a pre-mRNA expressed within the cells; a 3' spliced region comprising a branch point, a pyrimidine tract and a 3' spliced acceptor site; a 5' splice site; and a nucleotide sequence to be trans-spliced to the target pre-mRNA; wherein said nucleic acid molecule is recognized by nuclear splicing components within the cell and expression vector which expresses a nucleic acid molecule comprising the components listed above. The claims only from each other in that the claims of the instant application recite wherein the nucleic acid molecules are modified and synthetic whereas the claims of the US patent recite nucleic acid

molecules. Thus, the claims 1-30, 36-47, 50-52 of the instant invention falls entirely within the scope of the claims 19-34 of US patent 6,013,487. As the court stated in *In re Goodman*, 29 USPQ2d 2010 (CAFC 1993), " a second application-- "containing a broader claim, more generical in its character than the specific claim in the prior patent"--typically cannot support an independent valid patent. Miller, 151, U.S. at 198; See Stanley, 214 F.2d at 153. Thus, the generic invention, as noted above is "anticipated" by the species of the patented invention. Cf., Titanium metal corp. v. Banner, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985) (holding that an earlier species disclosure in the prior art defeats any generic claims). This court's predecessor has held that, without a terminal disclaimer, the species claims preclude issuance of the generical application. "*In re Van Ornum*, 686 F.2d 937, 944, 214 USPQ 761, 767 (CCPA 1982); *Schneller*, 397 F.2d at 354".

Conclusion

11. No claims are allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cynthia B. Wilder, Ph.D. whose telephone number is (571) 272-0791. The examiner works a flexible schedule and can be reached by phone and voice mail. Alternatively, a request for a return telephone call may be emailed to cynthia.wilder@uspto.gov. Since email communications may not be secure, it is suggested that information in such request be limited to name, phone number, and the best time to return the call.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Cynthia Wilder

CYNTHIA WILDER
PATENT EXAMINER

1/21/05